



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN THE APPLICATION OF:

ALAN A. RUBIN

CASE NO. 002

SERIAL NO.: 08/835,482

GROUP ART UNIT: 1615

FILED: APRIL 8, 1997

EXAMINER: BRIAN K.

SE IDLECK

FOR: IMPROVEMENT IN TREATMENT
OF PARKINSON'S DISEASE
AND RELATED DISORDERS BY
NOVEL FORMULATIONS OF THE
COMBINATION CARBIDOPA-LEVODOPA

DATED: MARCH 10, 2000

Asst. Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE TO EXAMINER'S
NOTIFICATION OF DEFECTIVE APPEAL BRIEF

A supplementary brief is submitted herewith, in triplicate, which, it is submitted, corrects the items listed by the Examiner. The Examiner's comments and suggestions are appreciated. A check in the amount of \$150.00 representing the fee required under 37 CFR 1.17(c) is also enclosed. The undersigned also ratifies the appeal brief previously submitted unsigned.

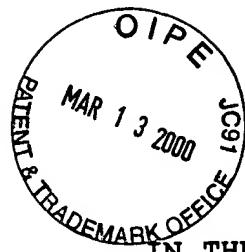
It is submitted that the new brief fully complies with 37 CFR 1.192(c) and should be entered. Such action is respectfully requested.

Respectfully submitted,

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BRIEF FOR APPELLANTS

Sir:

Real Party in Interest

The Real party of interest is the sole inventor, Alan A. Rubin, who has no obligation to assign, convey or license any rights in the invention.

Related Appeals and Interferences

There are no other appeals or interferences known to applicant which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Summary of the Invention

The appealed claims relate to a method for the therapeutic use of novel formulations of the combination carbidopa-levodopa in the treatment of Parkinson's disease.

Issues

All of the appealed claims (1 and 11-12) are rejected under 35 USC 103 as being unpatentable over the combined teachings

of Dempski et al (US Pat No 4,900,755, collectively "Dempski") and Conte et al (US Pat No 5,738,974, collectively "Conte").

Grouping of Claims

The ground of rejection, 35 USC 103, applies to all of the appealed claims (1 and 11-12).

Argument

The appealed Claims 1 and 11-12 have been rejected under 35 USC 103 as unpatentable over the cited references.

All of the claims are directed to the treatment of Parkinson's disease by administering novel formulations of the combination carbidopa-levodopa.

The examiner correctly states (paper 11) that "the combination of levodopa and carbidopa in a sustained release formulation is well known in the art". Dempski discovered a controlled release form of carbidopa-levodopa which prolonged pharmacologic activity and produced less variation in plasma levodopa levels than conventional carbidopa-levodopa (US Pat No 4,900,755, col. 2, lines 18-42). The present invention summarizes these beneficial effects in the specification at pp. 1 and 2 but also identifies a flaw in the Dempski formulation, i.e., the serious delay in onset of action of controlled release carbidopa-levodopa. Correction of this flaw via formulations which combine rapid onset with controlled release carbidopa-levodopa is clearly set forth in the passage on p. 2, lines 13-29 of the present specification and in the examples on pp. 3-5.

It is also the examiner's position, correctly, that "the prior art teaches formulation comprising multiple release layers to provide for immediate and sustained release of actives, including levodopa and carbidopa". Conte claims a tablet containing immediate and slow drug release components. In his specification (col. 2, lines 3-6), Conte states that "the prior art does not

envision the possibility of obtaining products capable of releasing one or more drugs at different rates or else of releasing two different drugs sequentially". And yet the prior art contains numerous examples of one or more drugs released at different rates and of two drugs released sequentially. For example, Lin et al (J. Int. Med. Res. 10(2): 126-128, 1982) describes the release of d-pseudoephedrine sulfate from the outer coat and inner core of a repeat action tablet and Nomeir et al (J. Clin. Pharmacol. 36(10): 923-930, 1996) report on the sequential release from 2-layer tablets of immediate release loratadine followed by extended release pseudoephedrine. Could Conte have been unaware of the prior art that invalidates the novelty of his release profile?

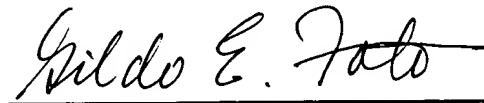
The examiner indicates that Conte "teaches a pharmaceutical tablet capable of releasing one or more drugs at different release rates.... The first contains one or more drugs with an immediate release profile and a second layer containing one or more drugs with a sustained release profile". But if the prior art covers this type of multiple release profile (see above), then Conte's novelty must lie elsewhere. The examiner also states that "Conte teaches combination therapy with both levodopa and carbidopa in a formulation with multiple release profiles". Yet Conte cites no valid, rational or original reason to use a multiple release format for carbidopa-levodopa. Instead, he repeats well known and established text book versions which describe (1) the metabolism of levodopa to dopamine (US Pat No 5,738,874, col. 2, lines 42-56) and (2) the use of carbidopa to inhibit peripheral decarboxylation of levodopa (US Pat No 5,738,874, col. 2, lines 57-65) to support the need for sequential release of carbidopa-levodopa (Goodman and Gilman's The Pharmacological Basis of Therapeutics, Pergamon Press, New York, NY, 8th Ed. pp. 466-472, 1990). Therefore, neither Conte nor Dempski have recognized the problem solved by this invention,

i.e., the rationale for immediate and long lasting therapeutic action of carbidopa-levodopa in Parkinson's disease. Recognition of an unrecognized problem militates for patentability.

If Conte's release profile and basis for utility are not novel, then the essence of his invention may relate to his formulations *per se*. In this regard, the formulations of the present invention differ significantly from those of Conte. For example, Conte claims a 3-layer tablet consisting of a first layer containing immediate or controlled release drugs, a second layer containing one or more drugs either equal to or different from the first layer and a third, rate-controlling barrier layer containing drug, if necessary.

The present invention teaches a bilayer or multilayer tablet as well as a capsule dosage form containing pellets. The bilayer and pellet (capsule) dosage forms are not included in Conte's patent; moreover, they comprise a sustained release core of carbidopa-levodopa overcoated only with an immediate release layer of carbidopa-levodopa. In addition, the multilayer tablets of the present invention contain an excipient layer which, unlike Conte's third barrier layer, may be drug-free and does not necessarily contain rate-controlling polymers. In view of the above argument, applicant submits that this application is in condition for allowance. Such action is respectfully requested.

Respectfully submitted,



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Certificate of Mailing - 37 CFR 1.8(a): I hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to: Ass't Commissioner for Patents, Washington, DC 20231 on March 9, 2000, adequate postage applied.

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APPENDIX

CLAIMS

What is claimed is:

1. A method for treating Parkinson's disease using an oral dosage formulation comprising an immediate release layer of 10-25 mg of carbidopa and 50-200 mg of levodopa and a sustained release layer of 25-75 mg of carbidopa and 100-400 mg of levodopa whereby, following administration, carbidopa and levodopa are available for rapid and sustained therapeutic action.

11. A method as claimed in Claim 1, the oral dosage formulation including a bilayer tablet or pellet, the latter to be administered in a capsule dosage form, comprising a sustained release core layer of carbidopa-levodopa overcoated by an immediate release layer of carbidopa-levodopa.

12. A method as claimed in Claim 1, the oral dosage formulation comprising a multilayer tablet wherein at least one sustained release layer of carbidopa-levodopa is separated from at least one immediate release layer of carbidopa-levodopa by an excipient layer which may be drug-free and does not necessarily contain rate-controlling polymers.